Efficacy of chlorhexidine rinses after periodontal or implant surgery: a systematic review

Solderer, Alex ; Kaufmann, Manuela ; Hofer, Deborah ; Wiedemeier, Daniel ; Attin, Thomas ; Schmidlin, Patrick R

Abstract: BACKGROUND: Biofilm management and infection control are essential after periodontal and implant surgery. In this context, chlorhexidine (CHX) mouth-rinses are frequently recommended post-surgically. Despite its common use and many studies in this field, a systematic evaluation of the benefits after periodontal or implant surgery is-surprisingly-still missing. OBJECTIVES: To evaluate the benefits of chlorhexidine rinsing after periodontal or implant surgery in terms of plaque and inflammation reduction potential. Furthermore, to screen whether the concentration changes or additives in CHX solutions reduce side effects associated with its use. MATERIALS AND METHODS: A systematic literature search was performed for clinical trials, which compared CHX rinsing after periodontal or implant surgery with rinsing using placebo, non-staining formulations, or solutions with reduced concentrations of the active compound. Four databases (Medline, PubMed, Embase, Cochrane) were searched up to June 2018. Two reviewers independently identified and screened the literature. RESULTS: From 691 titles identified, only eleven publications met the inclusion criteria and were finally included. Mainly early publications assessed the benefits of CHX over placebo rinsing, whereas more recent publications focused more on the evaluation of new formulations with regard to effectiveness and side effects. The use of CHX after surgery showed in general significant reduction in plaque (means of 29-86% after 1 week) and bleeding (up to 73%) as compared to placebo. No consensus, however, was found regarding the most beneficial CHX formulation avoiding side effects. CONCLUSION: Chlorhexidine rinsing helps to reduce biofilm formation and gingival inflammation after surgery. However, no additional reduction of periodontal probing depth over any given placebo or control solution could be found irrespective of whether CHX was used or not. The use of additives such as antidiscoloration systems (ADS) or herbal extracts may reduce side effects while retaining efficacy. CLINICAL RELEVANCE: Within the limitations of this review, it can be concluded that CHX may represent a valuable chemo-preventive tool immediately after surgery, during the time period in which oral hygiene capacity is compromised. To reduce the side effects of CHX and maintain comparable clinical effects, rinsing with less concentrated formulations (e.g., 0.12%) showed the most promising results so far.

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Solderer A[1], Kaufmann M[1], Hofer D[1], Wiedemeier D[2], Attin T[1], Schmidlin PR[1]

[1] Clinic of Preventive Dentistry, Periodontology and Cariology, Center of Dental Medicine, University of Zurich, Plattenstrasse 11, 8032, Zurich, Switzerland.

[2] Statistical Services, Center of Dental Medicine, University of Zurich, Switzerland

Alex Solderer
Alex.solderer@zzm.uzh.ch

Manuela Kaufmann
Manuela.kaumann@zzm.uzh.ch

Deborah Hofer
Deborah.hofer@zzm.uzh.ch

Daniel Wiedemeier
Daniel.wiedemeier@zzm.uzh.ch

Thomas Attin
Thomas.attin@zzm.uzh.ch

Patrick Schmidlin
Patrick.schmidlin@zzm.uzh.ch

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Abstract

Background: Biofilm management and infection control are essential after periodontal and implant surgery. In this context, chlorhexidine (CHX) mouth-rinses are frequently recommended post-surgically. Despite its common use and many studies in this field, a systematic evaluation of the benefits after periodontal or implant surgery is – surprisingly - still missing.

Objectives: To evaluate the benefits of chlorhexidine rinsing after periodontal or implant surgery in terms of plaque and inflammation reduction potential. Furthermore, to screen whether the concentration changes or additives in CHX solutions reduce side effects associated with its use.

Materials and Methods: A systematic literature search was performed for clinical trials, which compared CHX rinsing after periodontal or implant surgery with rinsing using a placebo, non-staining formulations or solutions with reduced concentrations of the active compound. Four databases (Medline, Pubmed, Embase, Cochrane) were searched up to June 2018. Two reviewers independently identified and screened the literature.

Results: From 691 titles identified, only eleven publications met the inclusion criteria and were finally included. Mainly early publications assessed the benefits of CHX over placebo rinsing, whereas more recent publications focused more on the evaluation of new formulations with regard to effectiveness and side effects. The use of CHX after surgery showed in general significant reduction in plaque (means of 29-86% after 1 week) and bleeding (up to 73%) as compared to placebo. No consensus, however, was found regarding the most beneficial CHX formulation avoiding side-effects.

Conclusion: Chlorhexidine rinsing helps to reduce biofilm formation and gingival inflammation after surgery. However, no additional reduction of PPD over any given placebo or control solution could be found irrespective whether CHX was used or not. The use of additives such as anti-discoloration systems (ADS) or herbal extracts may reduce side effects while retaining efficacy.

Clinical relevance: Within the limitations of this review, it can be concluded that CHX may represents a valuable chemo-preventive tool immediately after surgery, during the time period in which oral hygiene capacity is compromised. To reduce the side effects of CHX and maintain comparable clinical effects, rinsing with less concentrated formulations (e.g. 0.12%) showed the most promising results so far.

Keywords: Chlorhexidine - Periodontitis – Dental implant – Mouthwashes

Introduction

Oral biofilms are the main etiologic factor for the development of periodontitis and peri-implantitis [1]. In addition, wound healing after periodontal and implant surgery may be negatively affected by the presence of such biofilms [1]. Hence, a reduction or better elimination of biofilm is essential for restoring gingival tissues to a healthy state [1]. Especially after surgical interventions, plaque control by mechanical means is restricted and therefore must be achieved using other measures, such as antimicrobial strategies [2]. In this regard, chlorhexidine (CHX) has historically taken a key role in chemical biofilm control. It is a cationic bisbiguanide and has frequently been used in general medicine as a broad-spectrum antiseptic since 1953 [3]. It has proven to be an efficient agent against oral biofilms as well and displays antimicrobial activity against gram-positive and -negative bacteria, yeasts, and viruses, including human immunodeficiency virus (HIV) and hepatitis B virus [4]. The effect is dose-dependent. Whereas CHX is bacteriostatic at low concentrations, higher concentrations also exhibit a bactericidal effect [5,6]. CHX has been shown to penetrate biofilms as well, altering biofilm formation or having a direct bactericidal effect [7,8]. The mode of action is explained as follows: As the bacterial cell is negatively charged, the cationic CHX-molecule binds to the cell surface. The integrity of the bacterial cell is thereby altered in such a way that CHX can penetrate the inner cell membrane leading to a higher permeability. This results in leakage phenomena of low-molecular-weight components. At this point, the antimicrobial action is still at the bacteriostatic stage and can still be reversed if CHX is removed and the bacterial cell can recover. Stable or increasing CHX concentrations, however can lead to irreversible cell damage, i.e. cytoplasm coagulation and precipitation due to the formation of phosphate complexes such as adenosine triphosphate and nucleic acids [3,9].

Due to mostly negatively charged oral surfaces like teeth or the mucosa, CHX molecules display good adherence to these surfaces and thereby interfere with bacterial adhesion [5,10-13]. Further, CHX interacts with salivary glycoproteins. After rinsing with CHX, the saliva has been shown to exhibit an antibacterial activity for approximately five hours [14,15]. In addition, it has been suggested that CHX interferes with glucan production [16]. CHX binding to oral soft tissues allows substantivity for up to 12 hours [3]. Based on this mode of action and these properties, CHX is frequently used as mouth-rinse. The pharmacokinetics are favorable, as it is easy to reach an effective dosage of the active agent. Noteworthy, a mouth-rinse can be used independently of the patient`s ability to brush his teeth and is further well accepted by patients. This makes it an ideal preventive measure after surgical interventions, especially when

mechanical cleaning, for instance, is not possible or in clinical situations, in which mechanical plaque and inflammation control may be difficult due to discomfort or postoperative pain. However, this chemical plaque control is conceived for use on a short-term basis [3].

The clinically applied CHX concentrations mostly vary between 0.1–0.2 % and allow for reaching the ideal dosage of 18–20 mg per application. To reach a 20 mg dose with a 0.2 % concentration, 10 mL of solution must be applied for at least 30 seconds; with a 0.12 % concentration, 15 mL of solution must be applied for 60 seconds [3,17,18].

A beneficial clinical effect can already be observed with dosages of 5–6 mg, whereas dosages than 20 mg have been shown not to necessarily increase the effect. No adverse microbiologic changes, such as the overgrowth of opportunistic strains, when observing long-term use, have been reported so far, irrespective of the concentration used [19-21]. However, side effects must be taken into consideration [18]. In this context, temporary taste alteration [22,23], staining of teeth, mucosa and/or tongue [24] and increase in calculus formation [25] have frequently been described. Staining, however, remains the most common adverse side effect. The degree of staining seems to correlate with the frequency of consumption of chromogenic products such as coffee, tea, wine, and tobacco as well as with the concentration of CHX [26,27]. In recent years, research and development has focused on developing different methods to reduce staining while maintaining CHX efficacy. Recently mouth-rinses with lower concentrations and/or in combination with other ingredients such as herbal extracts or hyaluronic acid have been assessed in order to decrease such side effects [28-30]. A so-called anti-discoloration system (ADS) has also been implemented [31-34].

After periodontal and implant surgery, CHX mouth-rinses are most commonly prescribed. In 2017 a systematic review found it to be the most frequently used antiseptic agent after surgical intervention [35].
Despite the aforementioned disadvantages, chemical plaque control remains a must for most clinicians. An older study from Hemp et al. (1975), where gingival biopsies were taken at wound sites in dogs after plaque had been allowed to accumulate, showed a general increase in gingival inflammation [36].

Nevertheless, and surprisingly enough, only a few studies have evaluated the benefit of CHX-rinsing after periodontal or implant surgery and to the best of our knowledge, no systematic evaluation has been performed so far. Furthermore, systematic studies have not yet screened for optimal concentrations or compositions, which should be used to achieve optimal clinical

results with the least possible side effects. Therefore, this systematic review aimed for the first time to evaluate the benefit of CHX after periodontal or implant surgery compared to rinsing with a placebo and second to discern the influence of different concentrations and formulations in terms of efficacy, side effects and patient acceptance. We hypothesized, as shown for gingivitis prophylaxis and non-surgical periodontal therapy [37, 38-44], that rinsing with CHX

1) Results in less plaque formation and bleeding as compared to placebo control

2) Novel formulations are able to reduce side effects while still being effective, i.e. are as effective in plaque and bleeding reduction as the respective control (standard CHX-formulation).

Materials and Methods:

Protocols

A systematic literature search has been conducted and studies published from 1976 through June 2018 were included.

The review was conducted according to the **P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses (PRISMA) criteria. (Fig.1) The research question was assessed using the population, intervention, comparison and outcomes (PICO) method.

Two specific questions were addressed as follows according to the PICO principles:

1. In patients undergoing periodontal or implant surgery (**P**opulation), does Chlorhexidine rinsing as post-treatment protocol (**I**ntervention) have a beneficial effect on clinical periodontal parameters and healing (**O**utcome) compared to rinsing with placebo-solution (**C**ontrol)?
2. In patients undergoing periodontal or implant surgery (**P**opulation), does rinsing with reduced CHX-concentration or substitution by other adjuncts, as post-treatment protocol (**I**ntervention) have the same beneficial effect on clinical periodontal parameters and healing with less adverse effects (**O**utcome) compared to rinsing with placebo-solution (**C**ontrol)?

Search strategy:

The following databases were included: PubMed, MEDLINE, Embase and Cochrane library and the following MeSH terms were searched:

Population/Health condition: Periodontal OR Periodontitis OR Paradontitis OR Parodontitis OR peri-implant OR Periodontal Disease OR Periimplantitis

Therapy: Surgery OR GBR/ Guided Bone Regeneration OR GTR OR Guided Tissue Regeneration OR OFD OR Open Flap Debridement OR Widman Flap OR Modified Widman Flap OR Recession Coverage OR Root Coverage OR Implant Placement OR Implant Surgery OR Tunnel Technique OR Apical Positioned Flap OR Coronal Advanced Flap OR Split Flap OR Papilla Preservation Flap OR Distal Wedge OR Root Resection OR Tunnel Preparation OR Gingivectomy OR Root section

Mouth-rinse: Chlorhexidine OR Chlorhexidine Phosphanilate OR Chlorhexidine di-gluconate OR Chlorhexidine Gluconate OR Zinc-chlorhexidine OR CHX OR CHX Formulations

Screening and selection:

Two authors (A.S. and M.K.) independently searched and screened the publications by title and abstract. The inclusion and exclusion criteria for the studies were as follows:

Inclusion criteria were:

- Randomized Controlled Trials (RCTs) evaluating CHX-rinsing after periodontal or implant surgery
- Control group using a placebo, nothing or a different CHX-formulation
- Evaluation of efficacy (plaque and bleeding) and side-effects (staining)

Exclusion criteria were:

- In-vitro-studies
- Animal studies
- Non-RCT study designs

Available titles and abstracts were collected and discussed before being finally included or excluded. Inter-examiner agreement of a Cohen's kappa (K) of 0.6 was achieved after initial screening. Authors discussed discrepancies until reaching consent. If required, the senior author (PRS) was consulted.

The articles finally selected were analyzed as full texts (Fig. 1).

Studies were divided in two groups according to the type of question:

1) Results for plaque formation and bleeding, as compared to placebo control

2) Novel formulations are able to reduce side effects while still being effective, i.e. are as affective in plaque and bleeding reduction as the respective control

Data (plaque accumulation, bleeding on probing (BOP) and tooth-staining) was extracted by both reviewers separately.
Assessing the data, it was noted that the various studies used different scales and indices. Therefore, the authors agreed that the data be converted into a common unit, using percentage measurements in order to compare and interpret the results more easily.

Quality assessment

Quality assessment of the RCT`s using the Oxford quality scoring system by two authors (A.S. and M.K., Table 1) [45]. The Oxford scale assesses independently the methodological quality of a clinical trial judging the effectiveness of blinding described, the description of the randomization and drop-outs.
A score of between zero (very poor) and five (rigorous) scale is described.

Included studies received a 3- to 5-point score (max. 5 points) with a mean of 4.18. All eleven studies described randomized studies; three of which were not explicitly described as double-blinded [29, 30, 47] and three investigations were split-mouth trials [46, 47, 48].
In five trials, sample size calculation was performed and a statistical power of 80-85% could be reached [28,29,49,50,54].
A relatively low number of patients (9 to 53 patients) in some of the studies could be considered as a potential limitation of the results obtained.
Noteworthy was that seven of the eleven publications explicitly reported that they had no conflict of interests [28, 29, 30, 49, 50, 54, 61], whereas four studies did not mention this aspect [1, 46, 47, 48].

Outcome measures:

The main focus of this study was to filter out the benefits of a prescripted Chlorhexdine rinsing solution after periodontal or implant surgery on evaluation parameters such as plaque-index (PI) and bleeding-on-probing (BOP). In addition, changes in staining were tested. These primary outcomes were illustrated in different tables. Secondary parameter outcomes such as periodontal probing depth (PPD) and patient acceptance were described narratively since the data was very heterogenous.

Results

In this review, we evaluated the benefits of chlorhexidine rinsing after periodontal or implant surgery in terms of plaque and inflammation reduction potential as compared to a placebo (Table 2). Further, we screened whether concentration changes or additives in CHX solutions were able to reduce side effects. The results are presented separately in the following sections.

CHX vs. Placebo

Plaque

A summary of the plaque reducing potential of chlorhexidine after surgery as compared to placebo is depicted in Table 3. All four studies [1,46,47,48] assess the plaque reduction after rinsing with CHX and employ a placebo mouth rinse for comparison. Although CHX rinses are of different concentrations and vary between 0.12% [46,47] and 0.2% [1,48], all studies reported significantly less plaque accumulation with use of the CHX rinses as compared to the placebo groups. The reduction potential after 1 week ranged from 29% [1] to 86% [47]. After 2 weeks, it ranged between 50.9% [1] and 82% [48].

Gingival parameters

In terms of bleeding on probing (BOP) reduction, which was assessed in all four studies, the results ranged from 0% to 73% after 1 week (Table 4) [46,48]. Sanz et al. (1989) found that chlorhexidine led to a 16.8% and 10.3% reduction of gingivitis severity (average extent of the disease) after 4 and 6 weeks as compared to the control, respectively. With regard to gingival bleeding, CHX reduced the index score by about 40% after 4 and 6 weeks.
For wound healing and epithelialization, no statistically significant differences could be found, although the CHX group showed consistently better epithelialization [1].
Regarding sulcus bleeding index, Newman & Addy and Vaughan & Garnick also found a high statistical difference when CHX was used after surgery, compared to the placebo rinse, however this difference was no longer present after 1 and 3 months, when routine oral hygiene was re-instructed [46,47].

With regard to crevicular fluid flow rate during chlorhexidine-rinsing, no significant differences could be observed [47]. It was also found that CHX had no significant effect on the gingival inflammation parameters under periodontal dressings [48].

Probing Pocket depth

Two studies assessed the question, whether chlorhexidine rinsing could improve the clinical outcome after surgery as measured by periodontal pocket depth reduction resulting in a long-term effect. Irrespective of whether a chlorhexidine rinse was used or not they found that there was no additional benefit [1,46]. Therefore, no beneficial long-term effect could be seen from postoperative administrated CHX over placebo rinsing.

Patient acceptance

Overall patient compliance with CHX usage was not necessarily hindered by its side effects. CHX is known for several side effects, especially when used for longer periods.
Three out of four studies reported on these parameters. On the development of post-surgical pain, patients reported no advantage when using CHX. Also, there was no difference in the amount of pain medication used [1,47].
As expected, significantly more staining ($p = 0.017$) after the use of chlorhexidine was described by one study [1], which supports prior findings [24].
In a questionnaire, 67% of the patients liked and 24% disliked the taste of CHX [1].
The amount of self-perceived swelling was found to be greater in the CHX group ($p= 0.016$) [47].

Novel chlorhexidine formulations

CHX vs. alcohol-free CHX

An overview of included publications assessing different CHX-formulations is provided in table 5. The comparison of alcohol-free with alcohol-based solutions was described in two studies [49,61]. Alcohol-free CHX solutions have been introduced in an attempt to lower side effects. Alcohol is basically used to dissolve other compounds in the solution, and an antiseptic effect has also been discussed.
Olsson et al. 2012 carried out an RCT assessing the difference between alcohol-based CHX rinse and non-alcohol based CHX rinse on 20 patients after periodontal surgery. They did not find any significant differences in plaque-inhibition or amount of staining between the two solutions. This result agrees with findings of other non-surgical studies [49].
Both solutions were accepted equally well by the patients. Van Strydonck et al. reported, however, that patients preferred the taste of the alcohol-free CHX [50].
In 2018, Gkatzonis et al. conducted a study with 42 patients assessing the efficacy of both alcohol-based and alcohol-free solutions, as well as a third non-chlorhexidine solution (C31G). The trial resulted in significant superior plaque control of alcohol-based CHX over alcohol-free CHX and the third solution ($p < 0.001$). Despite showing no statistically significant differences in terms of post-surgical wound healing between the three solutions, it hints that the presence of alcohol may increase the efficacy of CHX in the early wound healing response (EHI = early wound healing index) [61].

CHX with ADS systems

Due to its main side effect of staining, and with it the possibility of reduced compliance, CHX mouthrinses with additional anti-discoloration-system (ADS) have been introduced. The combination of CHX with metabisulphite, peroxiborate, polyvinyl porrylidone and ascorbic acid has been described to interfere with pigmentation processes. While some studies have shown the ADS does not interfere with the antiplaque capacity of CHX [33] others studies have shown the opposite, that the addition of these substances reducing the efficacy of CHX [51]. The staining incidence has been shown in some studies to be significantly lower than without these additives [52,53], while other studies did not show any statistical differences [33,50].

Two RCTs specifically dealing with the use of CHX with anti-discoloration-system (ADS) after periodontal surgery were identified. In 2008, Cortellini et al. compared a 0.2% CHX rinse with a 0.2% CHX rinse with ADS. Bevilacqua et al. in 2016 additionally included 0.12% CHX in his comparative clinical trial. No differences could be found regarding efficacy of plaque inhibition and improvement of post-surgical healing in either study. In terms of staining, according to Cortellini et al. CHX with ADS showed clearly less pigmentations than the control CHX [50]. The CHX-solution with ADS was found to be better tolerated than the CHX without additives in both studies. Further it caused less alteration in food taste and salt perception than the control solution. Finally, the test CHX with ADS showed less irritation to the oral tissues. The adjunct of ADS could be of value after surgery where patient compliance is very important in terms of reducing microbial colonization in surgical sites. Bevilacqua et al. could not find any significant difference between the 0.2% CHX-, 0.2% with ADS- and 0.12%- groups tested regarding efficacy or staining [54].

Other CHX formulations

Genovesi et al. 2015 conducted an RCT with 40 patients after implant surgery comparing a 0.12 % CHX mouthwash to a 0.12% CHX plus hyaluronic acid mouthwash. The authors stated that hyaluronic acid in earlier studies seemed to be involved in the reduction of inflammation and in the promotion of re-epithelialization. The anti-oedematigenous effect of hyaluronic acid was confirmed in this study. Only 20% of patients treated with a hyaluronic acid additive showed edema, whereas 78% of the patient treated with only CHX showed edema at the surgical site after 2 days ($p = 0.0009$). In regards to anti-plaque and anti-gingivitis efficiency, no significant differences were noted by the authors. Further, both solutions showed no difference in the amount of staining produced [28].

Essential oils are known in medicine for their antimicrobial and anti-inflammatory properties. Gursoy et al. evaluated the effect of essential oils on periodontitis associated bacteria,

suggesting they inhibit growth of periodontitis-associated bacteria [55]. It was also demonstrated that plant extracts could inhibit the growth of oral biofilm similar to CHX.
A research group in the periodontology department at the University of Bern conducted two trials comparing 0.1% CHX and 0.05% CHX with herbal extract added after periodontal and implant surgeries in 2010 and 2015, the results of which support the above-mentioned theories [29,30]. No statistical differences were found for early wound healing, the reduction of probing pocket depth and reduction of the subgingival bacteria between the two solutions. While in the herbal extract group in both trials significantly lower tooth staining was observed, it could not be completely avoided. Even the ability to actively facilitate stain removal by the herbal extracts was discussed. Further, patients in the test group reported less loss of taste. The authors concluded that the lower concentration of CHX enhanced with herbal extracts may bring a benefit comparable to regular CHX solutions for long-term application.

Discussion

Chlorhexidine remains a widely and routinely prescribed rinsing solution after periodontal or implant surgery despite known side effects and interactions with healing [3]. This systematic review assessed the benefits of CHX after periodontal or implant surgery for the major clinical surrogate parameters of plaque, gingival inflammation and bleeding as compared to rinsing with a placebo. Further, the influence of different concentrations and formulations in terms of efficacy, side effects and patient acceptance were evaluated as well.
Eleven studies could be finally included in this review. Four studies compared the effect of CHX to a placebo solution whereas seven evaluated alternative CHX formulation in terms of clinical effectiveness and side effects. Despite the fact that CHX after surgery is part of the routine protocol employed in most practices, to the best of our knowledge, this review represents the first attempt to systematically assess the benefits of CHX-rinsing after periodontal or implant surgery. No systematic review has yet evaluated alternative CHX formulations in these indications as well. Systematic reviews on CHX in periodontology or implant dentistry have mainly focused on the benefits and risks after scaling and root planning to date [41,43]. Furthermore, only eleven clinical trials qualified for the inclusion in this review and evaluated post-surgical rinsing with CHX after periodontal or implant surgery and comparing this regimen with a placebo control.

It is well accepted, however, that rinsing with CHX after surgery represents a valuable adjunct in periodontal therapy in order to help patients reach a plaque-free or -reduced oral environment for optimized post-surgical healing, when mechanical cleaning at affected sites is not possible. Gartenmann et al. described Chlorhexidine as the most frequently used antiseptic agent used for 2 weeks following periodontal intervention [35].

Therefore, the results of this review may not be completely surprising. A meta-analysis of trials assessing CHX use after conventional SRP showed a slight but significant improvement of clinical attachment level and probing depth for patients rinsing with CHX over patients using a placebo solution [41]. These results are only partly reflected with the findings after periodontal surgery mentioned in this evaluation, where no significant improvement in pocket probing depth were found [1,46]. Beiswanger et al. published a study showing a mean plaque-reduction of 54% two and four weeks after conventional SRP and CHX mouth rinsing [56]. These results are comparable to the findings described after surgery. In 2017, James et al. published a systematic review that included 51 trials, about the benefit of CHX on gingival health.[57] An evaluation of the plaque indices in 12 different trials on 950 patients showed a large effect for CHX as compared to a placebo or no control rinse after 4 and 6 weeks. In terms of BOP/bleeding scores after initial SRP, a reduction of 48% in favor of CHX versus a placebo after two and four weeks was described previously [56]. In the review by James at al. the overall effect of CHX was judged as moderate (SMD -0.56) [57]. Results after surgery seem to be very similar, as found in the present review.

In the second part of this review, attention was paid to studies, which aimed to maintain or improve the CHX efficacy, while lowering side effects, by modifying the formulation. It was not surprising that the main side effects of tooth-staining and taste alterations were mentioned in most studies evaluated. The addition of a so-called anti-discoloration system (ADS) lowering the CHX concentration or supplementation with herbal extracts were the main measures to counteract possible side-effects. In general, results for these additives were contradictory. In addition, a comparable antibacterial effect was also not consistently achieved.

Regarding differences between alcohol- or water-based CHX formulations, the findings are inconsistant. While Olsson et al. state there are no differences regarding plaque control or wound healing [49], Gkatzonis et al. report a significant better plaque control by alcohol-based solutions [61]. Alcohol was not shown to alleviate the side-effects of CHX in the studies assessed.

With respect to the CHX concentration, lower concentrations (0.12%) displayed a similar clinical effectivity as the 0.2% concentrated solution. However, a lower concentration seemed to reduce

side effects [29,30]. Lowering CHX concentration, in combination with herbal extract additives, might be a good approach as shown in the few studies. In some trials, herbal extracts have been compared to CHX solutions, whereby slight clinical benefits were found [58-60]. No *in vivo* trials could be found evaluating a mixed herbal/CHX solution, however.
All RCTs reported clinical benefits when using CHX to prevent biofilm accumulation on non-shedding tooth surfaces after surgery, which supports the finding of studies that evaluated CHX-rinsing after initial SRP-treatment [47].

Additional trials are therefore still needed to definitively evaluate the benefits of rinsing with CHX after periodontal surgery or implant placement, as the number of clinical trials available are relatively small. This represents an essential limitation to our systematic review, despite the fact this topic is not at all new. Further, comparison of the results is difficult due to inconsistent outcome parameters and measurement techniques. Notably, different scales and indices were used in the various studies, despite the fact that most assessed comparable clinical situations and outcome parameters, i.e. plaque accumulation, gingival inflammation and wound healing. In addition, the observation periods varied widely between studies. A standardized comparison and meta-analysis was therefore not possible. Therefore, in order to identify an optimal spectrum of efficacy, with minimal side effects, additional clinical trials are still warranted.

Conclusion

Within the limitations of this systematic review, it can be concluded that CHX rinsing helps to reduce plaque accumulation and gingival inflammation after periodontal and implant surgery. On the short term, CHX is a valuable chemo-preventive tool, especially during the time period in which self-performed oral hygiene is compromised. However, as data from two studies (49 patients) has shown, current rinsing concepts have no positive effect on long term PPD reduction when compared to a placebo solution. Further, data from seven studies (247 patients) provided comparable clinical results when patients rinsed with reduced CHX concentrations (e.g. 0.12% vs 0.2%) in order to reduce side effects.

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Tables

Table 1

Quality assessment via Oxford quality scoring system [45].

	Sanz et al. 1989 [1]	Vaughan et al. 1989 [47]	Langenbaek 1976 [48]	Newman et al. 1981 [46]	Cortellini et al. 2008 [50]	Bevilacqua et al. 2016 [54]	Genovesi et al. 2015 [28]	Olsson et al. 2012 [49]	Duss et al. 2010 [29]	Laugisch et al. 2015 [30]	Gkatzonis et al. 2018 [61]
Described as randomized *	**1**	**Split-mouth/1**	**Split-mouth/1**	**Split-mouth/1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Described as double-blind *	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**1**
Randomization method described and appropriate **	**1**	**Split-mouth/1**	**Split-mouth/0**	**Split-mouth/1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Double-blinding method described and appropriate **	**1**	**0**	**0**	**1**	**1**	**0**	**1**	**1**	**0**	**0**	**1**
Drop-outs justified *	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
SCORE	**5**	**3**	**3**	**5**	**5**	**4**	**5**	**5**	**3**	**3**	**5**

* A study receives a sore of 1 for “yes” and 0 for “no”

** A study receives a sore of 0 if no description is given, 1 if the method is described and appropriate, -1 if the method is described is inappropriate

Table 2. Overview of the included publications comparing CHX to placebo.

Author	Rinsing Agent	Concentration	Intervention & Duration	Sample Size	Follow-up	Evaluation	Study Design
Sanz et al. 1989 [1]	CHX vs. Placebo	0.12%	Osseous periodontal surgery 2x/d 30 sec. for 6 weeks	40	1,2,4,6 weeks	• Plaque-Index • BOP • PPD • Epithelialization • Patients acceptance	RCT
Vaughan et al. 1989 [47]	CHX vs. Placebo	0.12%	Open flap debridement 2x/d for 2 weeks	9	1, 2 weeks	• Plaque-Index • BOP • Crevicular fluid flow • Pain/swelling	RCT Cross-over
Langenbaek 1976 [48]	CHX vs. Placebo	0.2%	Gingivectomy 2x/d for 3 weeks	24	1,2,3 weeks	• Plaque-Index • BOP	RCT
Newman et al. 1981 [46]	CHX vs. Placebo (NaCl)	0,2%	Inverse bevel flap 3x/d for 1 week	9	1 week, 1 and 3 months	• Plaque-Index • BOP • PPD • Patients acceptance	RCT Cross-over

Table 3. Reduction of plaque accumulation; CHX vs. Placebo.

Author	Rinsing Agent	Concentration	Follow-up	Mean Plaque-Index-reduction of CHX vs. Placebo	Significant reduction (overall)
Sanz et al. 1989 [1]	CHX vs. Placebo	0,12%	1 week 2 weeks 4 weeks 6 weeks	• 29% • 50.9% • 52.3% • 54.4%	yes
Vaughan et al. 1989 [47]	CHX vs. Placebo	0,12%	1 week 2 weeks	• 86% • 82%	yes
Langenbaek 1976 [48]	CHX vs. Placebo	0.2%	1 week 2 weeks 3 weeks	• 63% • 57% • 49%	yes
Newman et al. 1981 [46]	CHX vs. Placebo (NaCl)	0,2%	1 week	• 37%	yes

Table 4. Reduction of BOP; CHX vs. placebo

Author	Rinsing Agent	Concentration	Follow-up	Mean BOP- reduction of CHX vs. Placebo	Significant reduction (overall)
Sanz et al. 1989 [1]	CHX vs. Placebo	0.12%	4 weeks 6 weeks	• 41.6% • 40%	yes
Vaughan et al. 1989 [47]	CHX vs. Placebo	0.12%	1 week 2 weeks	• 58% • 60%	yes
Langenbaek 1976 [48]	CHX vs. Placebo	0.2%	1 week 2 weeks 3 weeks	• 0% • 10% • 16%	yes
Newman et al. 1981 [46]	CHX vs. Placebo (NaCl)	0.2%	1 week	• 73%	yes

Table 5. Overview of included publications assessing the most beneficial CHX-formulation.

Author	Rinsing Agent	Concentration	Intervention & Duration	Patient No.	Follow-up	Evaluation	Study Design
Cortellini et al. 2008 [50]	CHX vs. CHX + ADS	0.2% vs. 0.2% + ADS	Open flap debridement 2x/d for 1 week each (2 weeks)	47	1, 2 weeks	• Gingival parameters • Staining • Patients acceptance	Cross-over RCT
Bevilacqua et al. 2016 [54]	CHX vs. CHX + ADS	0.12% vs. 0.2% vs. 0.2% + ADS	Open flap debridement 1 week	53	1, 2 weeks	• Plaque Index • BOP • Staining • Patients acceptance	RCT
Genovesi et al. 2015 [28]	CHX vs. CHX + hyaluro-nic acid	0.12% vs. 0.12% + 0.1% hyaluronic acid	Implant placement 2x/d for 15 days	40	3h, 2d, 15d	• Plaque Index • BOP • Staining • Edema presence	RCT
Olsson et al. 2012 [49]	CHX vs. alk-free CHX	0.12%	Open flap debridement 2 weeks	20	2, 4 weeks	• Plaque Index • Patients acceptance	Cross-over RCT
Duss et al. 2010 [29]	CHX vs. CHX + herbal extract	0,1% CHX vs. 0.05% CHX + herbal extract	Open flap debridem-ent 4 weeks	45	2, 4, 12 weeks	• PPD • Staining • Bacteriological analysis	RCT
Laugisch et al. 2015 [30]	CHX vs. CHX + herbal extract	0,1% CHX vs. 0.05% CHX + herbal extract	Flap surgery for perio-treatment or Implant-placement. 2x/d for 2 weeks	40	1, 2 weeks	• Early wound healing • Staining • Patients acceptance	RCT

Gkatzonis et al. 2018 [61]	CHX vs. alk-free CHX vs. C31G	0.12%	Open flap debridement	42	1,2 weeks	• Early wound healing • Plaque Index • Bacterial count	RCT

Table 6. Plaque reduction after use of the different rinses.

Author	Rinsing Agent	Concentration	Patient No.	Follow-up	Plaque-reduction compared to baseline	Significant Difference Between Rinses
Bevilacqua et al. 2016 [54]	CHX vs. CHX + ADS	a. 0.12% b. 0.2% c. 0.2% + ADS	53	1 week 2 weeks	a. 4.8% b. 3.9% c. 3.8% a. 3.7% b. 3.9% c. 1.2%	No statistical difference
Genovesi et al. 2015 [28]	CHX vs. CHX + hyaluronic acid	a. 0.12% b. 0.12% + 0.1% hyaluronic acid	40	2 weeks	a. 16% b. 22%	No statistical difference
Olsson et al. 2012 [49]	CHX vs. alk.-free CHX	a. 0,12% b. 0.12% without Alk.	20	2 weeks 4 weeks	no baseline score assessed	No statistical difference
Gkatzonis et al. 2018 [61]	alk.-free CHX vs. CHX	a. 0.12% b. 0.12%	42	1 week 2 weeks	No baseline score assessed	Statistical significant

Table 7. Mean stain reduction; test rinses vs. control rinses.

Author	Rinsing Agent	Concentration	Patient No.	Follow-up	Mean reduction of staining in the test group	Significant Reduction (overall)
Cortellini et al. 2008 [50]	CHX vs. CHX + ADS	0.2% vs. 0.2% + ADS	47	1 week 2 weeks	• 52% • 37%	yes
Bevilacqua et al. 2016 [46]	CHX vs. CHX + ADS	0.12% vs. 0.2% vs. 0.2% + ADS	53	1, 2 weeks	• No percentage value calculable	no
Genovesi et al. 2015 [28]	CHX vs. CHX + hyaluronic acid	0.12% vs. 0.12% + 0.1% hyaluronic acid	40	2 weeks	• 12%	no
Duss et al. 2010 [29]	CHX vs. CHX + herbal extract	0,1% CHX vs. 0.05% CHX + herbal extract	45	4 weeks	• 21.1%	yes
Laugisch et al. 2015 [30]	CHX vs. CHX + herbal extract	0,1% CHX vs. 0.05% CHX + herbal extract	40	1 week 2 weeks	• 5% • 11%	no